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Experimental Studies of Stereotactic Laser Balloon Hyperthermic Treatment

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Background and Objective: **The hyperthermic treatment of small malignant brain tumors in basal ganglia and other eloquent cortical areas was investigated with a stereotactic Nd:YAG laser balloon unit.**
Study Design/Materials and Methods: **An Ultra Line™ fiber (Heraeus Laser Sonics, CA) was inserted into a 6 F silicone balloon catheter, which caused the laser beam to be directed 80° laterally. The balloon was inflated with physiologic saline to make the tumor tissue surrounding the laser fiber hypoxic. The hypoxia enhances the thermal effect on the tumor. The laser power was set at 5 watts (W) and a computer, programmed with specific parameters using feedback control was used to maintain the tissue 10 mm distant from the laser fiber at a temperature of 45°C. Forty five minutes of hyperthermic treatment was applied to an implanted subcutaneous glioma in a rat.**
Results/Conclusion: **The thermally induced damaged in the tumor appeared as a fan-shape lesion extending at a 100° angle from the laser beam axis. The entire tumor could be treated by rotating the laser fiber in the balloon catheter. Lasers Surg. Med. 20:195–201, 1997.**

Key words: laser; hyperthermia; Nd:YAG laser; balloon catheter

INTRODUCTION

The early diagnosis of brain tumors has been enhanced by the development of imaging technologies such as computed tomography (CT) and magnetic resonance imaging (MRI). However, small malignant tumors in the basal ganglia, or other eloquent cortical areas, are still difficult to treat. Commonly, a stereotactic biopsy is performed, and if histologic examination reveals a malignancy, radiotherapy, chemotherapy, and/or immunotherapy are instituted. Even with early application, these treatment modalities do not effect a complete cure.

Stereotactic laser hyperthermia may provide another treatment option for such cases. Here, we report a newly developed technique in stereotactic Nd:YAG laser balloon hyperthermic therapy.

MATERIALS AND METHODS

Technical Equipment

Balloon catheter. The effect of hyperthermia is enhanced by tissue ischemia at the laser fiber tip. This also protects the tip from carbonization [1]. A 7 French shaft balloon catheter (Kaneka Medica Co., Japan) can be made from a 0.22 mm silicon sheet (hardness, shore A = 20) to accommodate the quartz laser fiber. The balloon is located at the tip of the catheter and measures 6 mm in length and 1.7 mm in diameter (Fig. 1a). After inflation with 0.6 ml of saline, the balloon reaches 15.9 mm in length, 8.2 mm in diameter, and 0.04 mm in thickness (Fig. 1b). It is heat resistant up to 200°C and is 98% translucent to Nd:YAG laser irradiation.

Optical fiber. The Ultra Line™ fiber (Heraeus Laser Sonics, CA.) is a 600-μm quartz fiber integrated into a fused quartz probe containing angled optics that transmit the laser beam laterally at an angle of 80° (Fig. 2a,b). This fiber is

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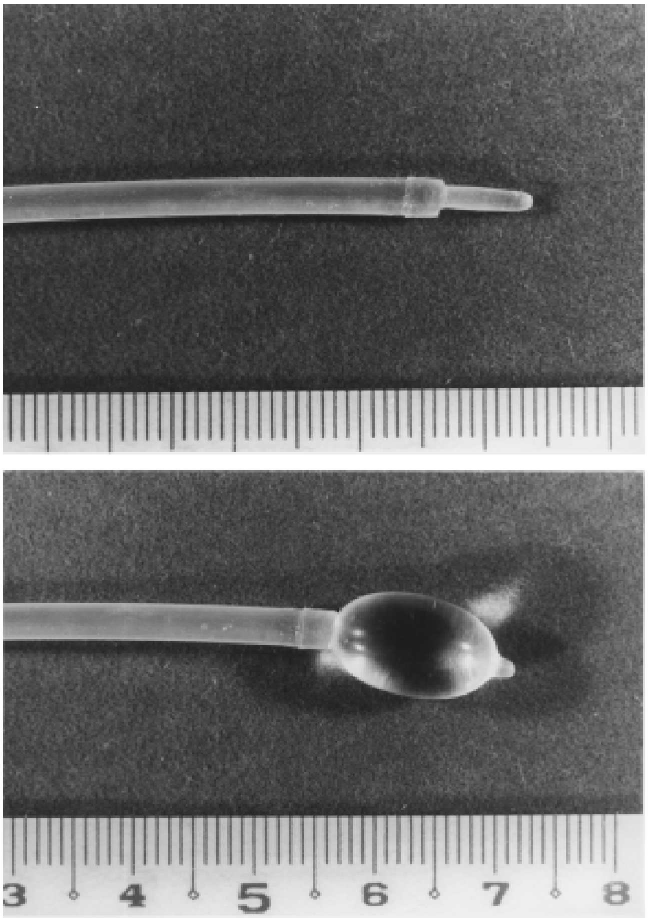

Fig. 1. (**a**) 7 F silicon balloon catheter. (**b**) Balloon inflated with 0.6 ml saline.

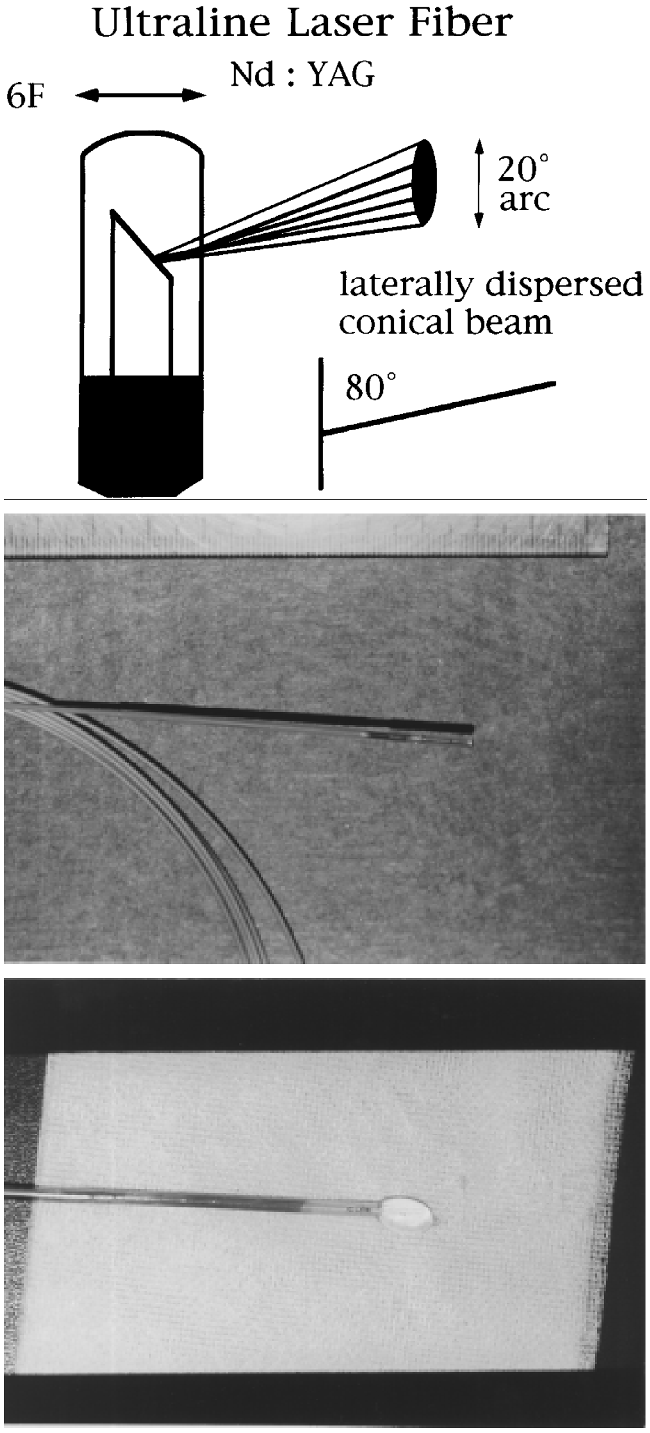

Fig. 2. (**a**) Diagram for Ultra Line™ Laser Fiber optics. (**b**) Laser fiber. (**c**) Laser balloon probe.

placed into the three-way stop cock of the balloon catheter (Fig. 2c). The direction of the laser beam can be controlled by rotating the fiber at its insertion point.

Laser. A Nd:YAG laser (Heraeus Laser Sonics) with a wavelength of 1.064 µm was used. Its in vivo power delivery was 5 W, and it had been modified to include a computer-controlled optical shutter. A feedback mechanism was used to control the treatment parameters so that the tissue 10 mm from the tip of laser fiber was kept at a temperature of 45°C. The laser pulsed on and off every half second (0.5 second on, 0.5 second off) [2,3].

Measurement of Tissue Temperature

Three copper-constantan thermometry probes (0.6 mm in diameter) were either inserted to a depth of 16 mm into the cortex or the tumor surface. Each probe was placed in the path of the laser beam 10 mm, 15 mm, and 18 mm from the probe. Another thermometry probe was placed in the balloon. The temperature feedback system stopped the laser output when the tissue 10 mm distant from the laser probe reached 45°C.

Blood Flow during Balloon Inflation

The change in blood flow in the tumor tissue around the balloon was measured with a Laser Flowmeter (Model LBF-3, Biomedical Science Co., Tokyo, Japan) inserted to a depth of 16 mm from the tumor surface and 10 mm from the axis of the probe.

Hyperthermic Treatment

In vivo. For acute and subacute stage experiments, three Japanese white rabbits, weighing 3.0–4.0 kg, were anesthetized with an intramuscular injection of Ketalar (20–40 mg/kg body weight) and an intravenous injection of pentobarbital (10–30 mg/kg). The rabbits were placed in the sphinx position with their heads fixed to a stereotactic frame. A midline skin incision was made on the vertex of the skull, and a craniectomy was made with a rongeur. A wide dural opening exposed both hemispheres.

The laser balloon probe was inserted to a deapth of 16 mm into the left occipital lobe. The thermometer probes were placed into the cortex at 10 mm, 15 mm, and 18 mm points parallel to the axis of the laser probe and directed anteriorly toward the frontal lobe. The balloon was inflated with 0.6 ml of saline. During the 15 minutes of laser application, the temperature changes at the three points were recorded continuously. The rabbits were later killed with a pentobarbital overdose, and the brains were removed and examined microscopically.

Earlies experiments were performed on large subcutaneous gliomas in a rat model. Sixteen rats weighing 300–350 g received a subcutaneous injection of rat glioma cells (RGC6-CL2) in their backs. Two months later, large tumors (5 × 3 × 4 cm) were visible (Fig. 3a). Acute and subacute hyperthermia experiments were performed on these tumors.

The acute hyperthermia experiments were performed on four rats that were anesthetized with an intraperitoneal injection of sodium pentobarbital (40–60 mg/kg body weight) and inhalation of halothane (1.0–2.0% Fluothane). The rat was placed in the sphinx position, and the back was shaved to expose the subcutaneous tumor mass. The laser balloon probe was inserted into the tumor (16 mm deep), and the thermometer probe was implanted 10 mm away parallel to the laser probe (Fig. 3b). The laser balloon was inflated with 0.6 ml saline and the laser irradiated for 45 minutes to a maximum temperature of 45°C. The total dose was between 6,500–7,200 joules. The blood flow 10 mm distant from the probe was examined. The rats were killed with an ether overdose, and the tumors were removed for microscopic examination.

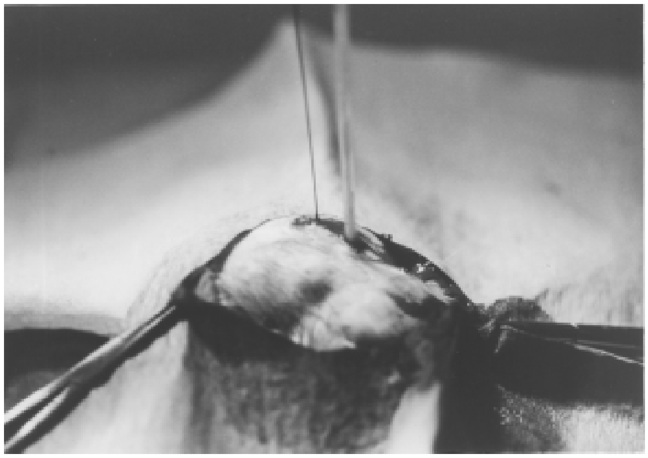

Fig. 3. (**a**) Implanted subcutaneous rat glioma after 2 months. (**b**) Hyperthermia treatment in progress.

Six other rats underwent the same operation. Four were kept alive for 5–7 days and two were kept alive for 14 days prior to being killed. The effects of subacute hyperthermia was examined in these animals.

A further four rats underwent the same operation with the probe alone without the balloon attached. These were kept alive for 5–14 days. Another two rats underwent the same operation with the laser balloon inflated with 0.6 ml saline but without laser radiation delivery. These animals were kept alive for 14 days.

RESULTS

The inflation of the laser balloon caused the rabbit's brain to bulge slightly from the craniec-

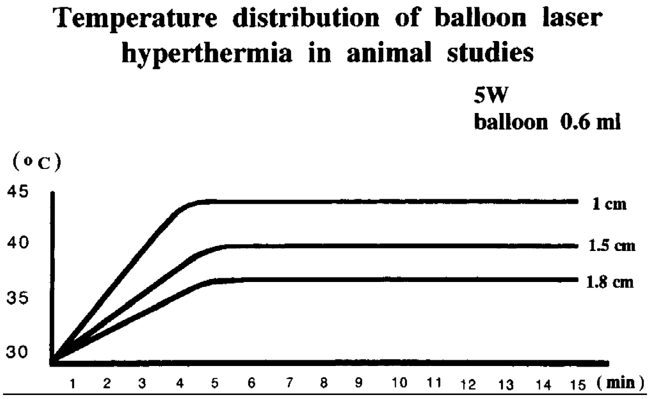

Fig. 4. In the rabbit's brain, the temperature 10 mm distant from laser fiber was 45°C after 4 minutes and 10 seconds. At 15 mm it was 39°C after 5 minutes, and at 18 mm it was 37°C after 5 minutes and 10 seconds. Each temperature was maintained for 15 minutes during hyperthermic therapy.

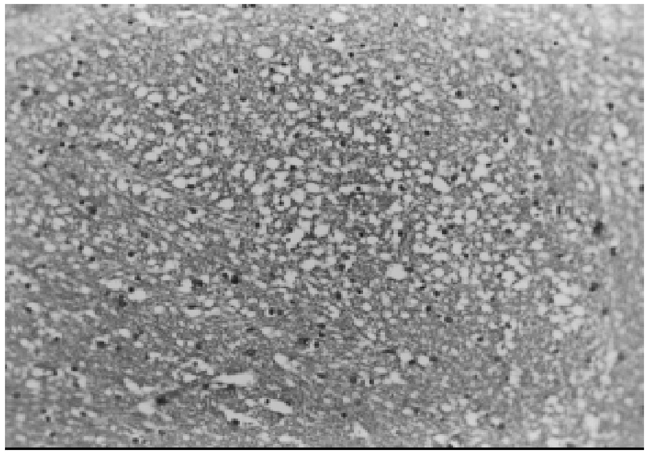

Fig. 5. Hematoxylin eosin stain (×50) of rabbit brain tissue. After 15 minutes of hyperthermia at 45°C, edema is prominent.

tomized window. However, there were no changes in spontaneous respiration, pulse rate, or pupil size during the operation.

A correlation between tissue temperature and distance from the laser probe was noted. The temperature 10 mm away was 45°C after 4 minutes and 10 seconds; at 15 mm it was 39°C after 5 minutes, and at 18 mm it was 37°C after 5 minutes and 10 seconds. Each temperature remained constant for the 15 minutes of hyperthermia (Fig. 4). The temperature inside the balloon reached 52°C after 8 minutes and 15 seconds, and it remained at this temperature throughout the hyperthermia. The tissue was examined and found to be edematous within 10 mm (Fig. 5), but there were no pathologic findings distant to this area. The thermal conduction time was calculated, and the associated histologic findings in normal rabbit brain were noted.

The thermal damage to the rat subcutaneous glioma (acute stage) can be clearly seen 10 mm away from the probe (Fig. 6). However, at this distance tumor cells remained intact. Balloon inflation caused a 45% decrease in blood flow at 10 mm point from the probe when compared to balloon deflation (Fig. 7).

After subacute hyperthermic treatment of the rat glioma, the coagulated tissue layer was visible as a fan-shape area 10 mm thick lying at a 100° angle to the projection of the laser beam (Fig. 8). The border of the treated tissue showed a well-demarcated wave-like zone. Tumor cells within the area show marked thermal damage (Fig. 9). The 14th day lesion displayed histologic findings

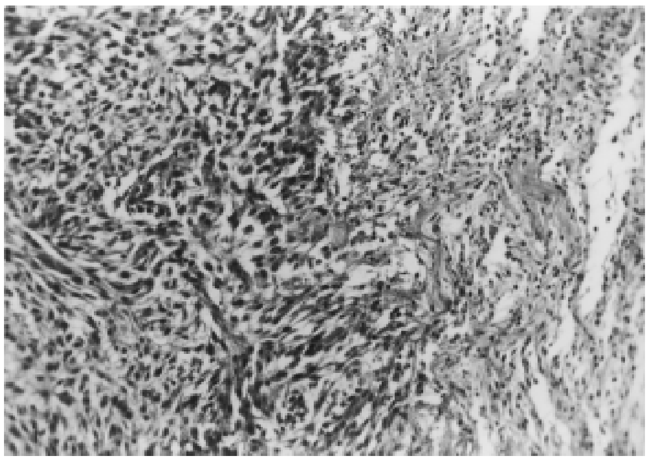

Fig. 6. Hematoxylin eosin stain (×50) of the subcutaneous glioma. The thermally damaged tissue can be seen on the right side.

which were almost the same as those seen on the 5–7th days.

Treatment without the balloon produced different findings. The coagulated tissue layer was almost the same as that seen with the laser balloon, but the border zone of tissue was unclear and the tumor cells around the vessels were almost intact (Fig. 10).

Treatment with balloon inflation alone produced no particular findings other than macrophage infiltration around the laser probe's hole.

DISCUSSION

Various reports in the neurosurgical literature have concerned the clinical application of hy-

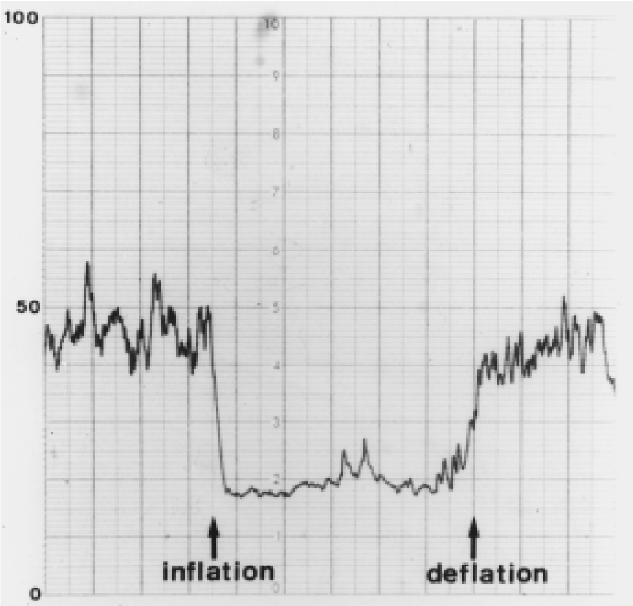

Fig. 7. Tumor blood flow 10 mm distant from the laser fiber decreased by 45% after balloon inflation with 0.6 ml saline.

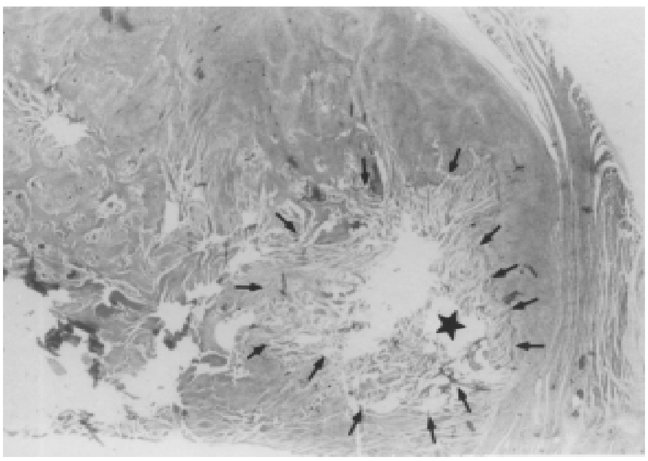

Fig. 8. Subcutaneous rat glioma after 5 days of hyperthermia treatment. This axial slice shown the laser balloon probe position (★). The laser beam was oriented in the direction of 10 o'clock. Arrows indicate the zone of coagulation. Fan-shaped thermal coagulation layers were confirmed (10 mm thickness and at a 100° angle).

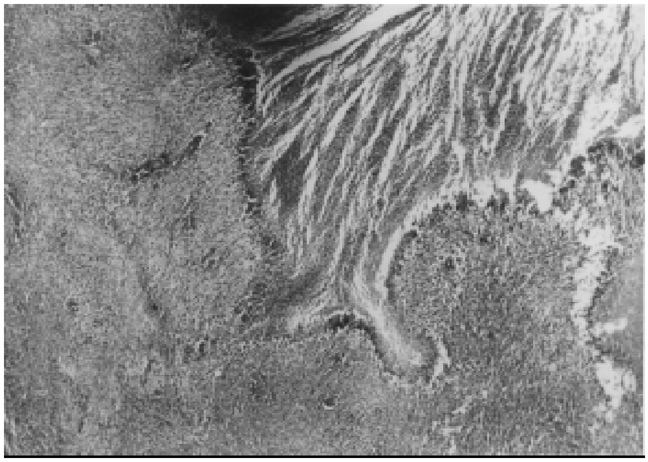

Fig. 9. Hematoxylin eosin stain (×40). The border of hyperthermically treated tissue shows a wavelike and well-demarcated zone (arrow).

perthermia [4–7]. Many methods of tissue heating have been investigated, including the heat lamp, perfusion with heated blood, high-frequency electric currents, ultrasound, and electromagnetic radiation in both the radio- and microwave frequencies [8]. Laser irradiation of tumor tissue is a recently introduced modality for inducing hyperthermia with the potential for better selectivity and control than has been achieved with conventional heat sources. Laser wavelength is a key factor in this therapeutic approach as the energy absorbed by tissue chromophobes is directly responsible for the heating effect [9,10]. The penetration depth for irradiation from the Nd:YAG laser at the 1,064 μm wavelength is in the range of 3–8 mm (δ) [11]. The Nd:YAG laser can be delivered via a fiber optic probe inserted through the stereotactic biopsy channel of a cannula, and therefore it has great potential for the stereotactic hyperthermic treatment of small and deep-seated malignant tumors.

In general, the steady-state temperature distribution in irradiated tissue is determined by five parameters: thermal conductivity, specific heat, blood flow, optimal penetration depth, and optical reflection [11]. Vascularity is especially important because blood perfusion may change during hyperthermic treatment [12,13]. Local hyperthermia in normal monkey brain causes the regional cerebral blood flow to increase linearly at the rate of 10% per 1°C temperature rise. When brain tissue is heated to 45°C for 40 minutes, the rate of cerebral blood flow (rCBF) increases to a peak value of 2.6 times the preheated value [14]. Studies on solid tumors in vivo also have shown an increased sensitivity of tissue to heat under hypoxic conditions [15–17]. We used the Ultra Line™ fiber (Heraeus Laser Sonics), with a Nd: YAG laser, which transmits the laser beam conically outward at 80° to the axis of projection. We introduced a new laser balloon probe to reduce regional blood flow and so create a hypoxic state around the tip of the laser probe during the hy-

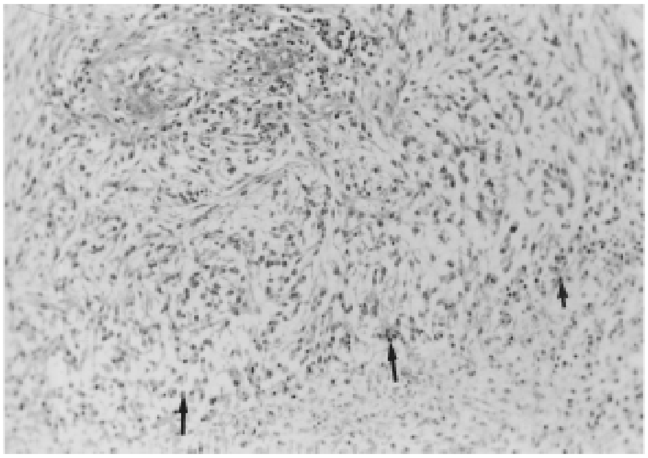

Fig. 10. Hematoxylin eosin stain (×20). Rat's subcutaneous glioma after 5–7 days of hyperthermic treatment using the laser probe without the balloon attached. The thermal coagulation layers (arrow) are unclear and the tumor cells around the vessels are almost intact.

perthermia treatment. Inflation of the laser balloon with 0.6 ml saline caused the balloon to become 8.2 mm in diameter and 15.9 mm in length. During inflation of the balloon, a 4 mm thickness of tumor and/or normal tissue was compressed. The rCBF in the tumor 10 mm distant from the laser fiber showed a 45% decrease.

Histologic evaluation of the tumor did not reveal blood vessels within 10 mm from the laser balloon probe. The coagulation layer was also clearly demarcated. The same operation without balloon inflation showed unclear coagulation layers and intact tumor cells around the blood vessels.

Laser Power, Temperature, and Thermal Dose

The laser power used in the hyperthermic treatment was between 1 W and 5 W [2,18–20]. Five watts of laser power was the optimum to reach 45°C. This temperature was achieved within 4 minutes and 10 seconds at the 10 mm mark. Ten watts would have caused perforation of the silicon balloon.

There are many reports describing the results of hyperthermia treatment. Interstitial microwave hyperthermia of the canine brain required a thermal dose of 43–45°C measured 5 mm from the antenna junction applied for 30–60 minutes to induce necrosis [21]. Histologic tissue necrosis and a low density lesion on CT scan were seen in a normal monkey brain near the site of heating at 44°C for 30 minutes [22]. Waldow [23] has described Nd:YAG laser-induced hyperthermia in a mouse tumor model of SMT-F mammary carcinoma. For these small tumors, a 5-week complete response rate exceeding 50% required a 45 minutes laser treatment at 45°C. After 5–7 days or 14 days of hyperthermic treatment, our histologic findings showed an area of fan-shaped coagulation necrosis and a well-demarcated border zone in the laser beam path. Stereotactic hyperthermia using a laser balloon probe is a potentially useful modality for treating small malignant gliomas less than 10 mm in diameter.

CONCLUSIONS

The Nd:YAG laser and the Ultra Line™ fiber and silicon balloon catheter are effective in the treatment of subcutaneous gliomas. The laser fiber in the balloon catheter can be manipulated to alter the direction of the laser beam at will. These experiments support the use of this method in the stereotactic treatment of deep-seated small malignant gliomas.

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REFERENCES

1. Shimamura Y, Gunven P, Ishii M, Kitai S, Ono M, Okajima K, Shima Y, Ikuta S, Takahashi A, Kitaya T, Matsuyama T: Endoscopic laser coagulation through an optical laser balloon. Lasers Surg Med 1990; 10:25–27.
2. Panjehpour M, Overholt BF, Milligan AJ, Swaggerty MW, Willkinson JE, Klebanow ER: Nd:YAG laser-induced interstitial hyperthermia using a long frosted contact probe. Lasers Surg Med 1990; 10:16–24.
3. Panjehpour M, Wike AV, Frazier DL, Overholt BF: Nd: YAG laser hyperthermia treatment of rat mammary adenocarcinoma in conjunction with surface cooling. Lasers Surg Med 1991; 11:356–362.
4. Kobayashi T, Kida Y, Matsui M, Amemiya Y: Interstitial hyperthermia of malignant brain tumors using implant heating system (IHS). Neurol Surg (in Japanese) 1990; 18:247–252.
5. Marchosky JA, Moran CJ, Fearnot NE, Babbs CF: Hyperthermia catheter implantation and therapy in the brain. J Neurosurg 1990; 72:975–979.
6. Bettag M, Ulrich F, Schober R, Furst G, Langen KL, Sabel M, Kiwit JCW: Stereotactic laser therapy in cerebral gliomas. Acta Neurochir Suppl 1991; 52:81–83.
7. Takahashi H, Tanaka R, Hondo H, Nakajima T, Watanabe M, Sekihara Y, Kakinuma K: Clinical experiences of RF hyperthermia for malignant brain tumors. Neurosurgeons 1993; 12:245–255.
8. Song CW: Effect of hyperthermia on vascular functions of

normal tissues and experimental tumors. JCI 1978; 60: 711–713.
9. Matsumoto R, Seling AM, Colucci VM, Jolesz FA: Interstitial Nd: YAG laser ablation in normal rabbit liver: Trial to maximize the size of laser-induced lesions. Lasers Surg Med 1992; 12:650–658.
10. Hara M, Takeuchi K, Fujii Y, Maemura E, Konishi Y: Experimental studies using laser angioplasty combined with balloon angioplasty for stenotic cerebral lesions. J Clin Laser Med Surg 1991; 11:453–457.
11. Svaasand LO, Boerslid T, Oeveraasen M: Thermal and optical properties of living tissue: Application to laser-induced hyperthermia. Lasers Surg Med 1985; 5:589–602.
12. Hahn GM: Metabolic aspects of the role of hyperthermia in mammalian cell inactivation and their possible relevance to cancer treatment. Cancer Res 1974; 34:3117–3123.
13. Storm FK, Harrison WH, Elliott RS, Morton DL: Normal tissue and solid tumor effects of hyperthermia in animal models and clinical trials. Cancer Res 1979; 39:2245–2251.
14. Moriyama E: Cerebral blood flow changes during localized hyperthermia. Neurol Med Chir (Tokyo) 1990; 30: 923–929.
15. Suit HD: Hyperthermic effects on animal tissues. Rad Biol 1977; 123:483–487.
16. Hill SA, Denekamp J: The effect of vascular occlusion on the thermal sensitization of a mouse tumour. Br J Radiol 1978; 51:997–1002.
17. Nielsen OS: Effect of fractionated hyperthermia on hypoxic cells in vitro. Int J Radiot Biol 1981; 39:73–82.
18. Masters A, Steger AC, Lees WR, Walmsley KM, Bown SG: Interstitial laser hyperthermia: A new approach for treating liver metastases. Br J Cancer 1992; 66:518–522.
19. Schober R, Bettag M, Sabel M, Ulrich F, Hessel S: Fine structure of zonal changes in experimental Nd:YAG laser-induced interstitial hyperthermia. Lasers Surg Med 1993; 13:234–241.
20. Ji Y, Walstad D, Brown JT, Powers SK: Interstitial photoradiation injury of normal brain. Laser Surg Med 1992; 12:425–431.
21. Matsumoto K, Stauffer PS, Fike JR, Gutin PH: Hyperthermia for malignant brain tumors: Development of an interstitial microwave hyperthermia system and study of thermodosimetry and heat toxicity in a canine brain model. Neuro Surg (in Japanese) 1986; 14:965–972.
22. Nakagawa M, Matsumoto K, Higashi, Furuta T, Ohmoto T: Acute effects of interstitial hyperthermia on normal monkey brain: Magnetic resonance imaging appearance and effects on blood-brain barrier. Neuro Med Chir (Tokyo) 1994; 34:668–675.
23. Waldow SM, Morrison PR, Grossweiner LI: Nd:YAG laser-induced hyperthermia in a mouse tumor model. Lasers Surg Med 1988; 8:510–514.